08/442,288

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EXAMINER
SMITH,L

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892. 2 page
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☒ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-12 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☒ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☒ been filed in parent application, serial no. 08/356,372 ; filed on 5/16/95.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

15. The disclosure is objected to because of the following informalities: page 2, line 1 insert "it" between "that" and "is", page 2, line 37, molecules should be singular, page 4, line 2, antibodies should be singular, page 11, line 30, "supematant" should be "supernatant". The claims should begin with "I claim", "We claim" or "What is claimed is". Appropriate review and correction of the entire specification are required.

16. This application does not conform with the rules governing applications because the specification should be written on but one side of the paper only. See MPEP 608.01 and 37 CFR 1.52(b) and (c) and accompanying PTO Form 152. Appropriate correction is required.

17. Claims 8 and 9 are rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. Claims 8 and 9 are drafted in terms of "use". However, "use" is not one of the statutory classes of invention. See Clinical Products v. Brenner, 149 USPQ 475.

Additionally, claims 8 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the claims do not recite positive active steps so that the claims will set out and circumscribe particular area with reasonable degree of precision and particularity and make clear what subject matter

the claims encompass, as well as make clear the subject matter from which others would be precluded. See Ex parte Erlich, 3 USPQ2d 1011 (BPAI, 1987). However, claims 8 and 9 will be examined as depending from claim 1.

18. Claims 1-12 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12 of copending application Serial Nos. 08/442,286 and 08/356,372. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

19. Claims 6, 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to an antigenic composition of glycoprotein D and CS protein in combination with the adjuvants 3D-MPL and QS-21, a method of making an antigenic composition and a method of stimulating cytolytic T cell and gamma interferon production. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The claims are broadly drawn to a vaccine composition comprising antigen derived from all viral, bacterial or parasitic infections as well as to human immunodeficiency virus and feline leukemia virus. The specification lacks enablement for vaccine compositions which would be effective against all of the claimed species of pathogenic infections, particularly against HIV, prophylactically or therapeutically. The specification provides no probative evidence to support a vaccine which would protect

humans against AIDS. The obstacles to vaccine development and therapeutic approaches with regard to retroviruses associated with AIDS in humans are well documented in the literature. These obstacles include: 1) the extensive genomic diversity associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert form, as well as via free virus transmission, 3) existence of a latent form of the virus, 4) the ability of the retrovirus to "hide" in the central nervous system where blood cells and neutralizing agents carried by the blood cannot reach the retrovirus, due to the blood-brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these obstacles establish that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any vaccine or any immunization treatment or any therapeutic regimen on its face. In order to enable claims to drugs, antigenic compositions and their uses, either in vivo or in vitro data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the proposed claims are sufficiently enabled. See In re Irons, 340 F.2d 924, 144 USPQ 351 (CCPA 1965), Ex parte Krepelka, 231 USPQ 746 (PTO Bd. Pat. App. & Inter. 1986) and Ex parte

Chwang, 231 USPQ 751 (PTO Bd. Pat. App. & Inter. 1986). By definition vaccines must not only induce an immune response, but must be immunogenic to the extent that upon subsequent challenge with the live virus, development of the disease is prevented, or better yet infectivity does not occur.

The development of immune responses important in protection against HIV infection has not been established. Generally it is thought that humoral immunity as well as cell mediated immunity are important in recovery from viral infections. The generation of neutralizing antibody responses against HIV have not been well correlation with slowing or preventing HIV infection. Cohen et al have reported that neutralizing antibodies have been unable to neutralize what is known as "primary field isolates" of HIV, which isolates are more closely related to that which would infect the general population (page 980). Similarly the development of cytolytic responses has not been correlated with the slowing of progression to HIV disease. Butini et al, in comparing CTL activity in lymphoid tissue and peripheral blood found HIV-specific CTL activity in a patient with rapidly progressive disease, while in another patient showing no progression of immunodeficiency, no CTL activity (abstract J306). Thus it is not clear what factors or parameters constitute immunity to HIV disease. Additionally, the claims are drawn to vaccine compositions against feline leukemia virus. This virus

appears to be a virus specific to the feline animal species while the others appear to cause infections in humans. The specification lacks enablement for the claimed adjuvant compositions and the feline leukemia virus and enablement to show that the claimed adjuvants are effective in the feline animal species. In view of all of the above and in view of the lack of guidance provided by the specification with respect to the enablement of the broad claims, it is determined that the specification is not commensurate in scope with the claimed subject matter.

20. Claims 1-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The language of the claims is not as precise as the subject matter permits such that one may reasonably know what will infringe and what will not infringe the claims. The claims are indefinite in the recitation of "an antigen: an antigenic composition and combinations thereof" because it is not clear what the difference is between antigen and antigenic composition and to what "combinations thereof" is referring. Does the composition contain two antigens or does the antigen contain an antigenic composition? It is unclear what applicant intends by "safe" amount of a vaccine. There is no

recovery step in the process for making a vaccine (claim 12). Clarification is required in order to obviate this rejection.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

22. Claims 1, 2, 5, 6, 8, 10 and 12 are rejected under 35 U.S.C. § 103 as being unpatentable over Long et al, 1984 in view of Kensil et al, U.S. Pat. No. 5,057,540 and further in view of Schneerson et al, 1991. Long et al describe the protection of mice from lethal challenge with herpes virus, after administration of herpes virus glycoprotein D in adjuvant

(abstract and table 1). The administration of glycoprotein D conferred protection against lethal challenge with both homologous and heterologous virus types (page 763, first column). Glycoprotein D generated high levels of neutralizing antibody titres (pages 761-763 and table 1). Long et al differ from the claimed invention in not specifically describing the use of QS-21 or 3D-MPL in the antigenic composition.

Kensil et al teach compositions of saponins and antigens and the effectiveness of saponins (from *Quillaja saponaria* bark) such as QA-21, QA-17 and QA-18 as adjuvants in antigenic compositions (abstract, figures 12-15 and columns 20-23). Saponins are natural products and may be used as immune adjuvants (col. 3, lines 8-46). The effective ratios of adjuvant to antigen suggested are "3.0 or less or preferably 1.0 or less" (col. 7, lines 10-13). The saponins, particularly QA-21 (col. 5, lines 30-35) which appears to be similar or an obvious or analogous variant of the claimed QS-21, may be administered individually or admixed with other substantially pure adjuvants to "achieve the enhancement of the immune response to an antigen" (col. 7, lines 14-20). While Kensil, et al suggest the use of QA-21 in admixture with other adjuvants, Kensil et al do not specifically describe 3-De-O-acylated monophosphoryl lipid A (3D-MPL) as an adjuvant. However, Schneerson et al describe the enhancement of serum antibody responses in mice to polysaccharide

antigens in combination with MPL as adjuvant (abstract, page 213, tables 1-6). Antigen in combination with MPL, which MPL appears to be similar or an obvious or analogous variant of the claimed 3D-MPL, when administered, generated higher specific serum antibody responses. Schneerson et al also describe compositions of MPL and other adjuvants with antigen at ratios of 1:1 (page 213, tables 2-5). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include QS-21 and 3D-MPL in an antigenic composition with antigen as suggested by Kensil et al and Schneerson et al. It would have been expected, barring evidence to the contrary, that the addition of QS-21 and 3D-MPL to glycoprotein D subunit vaccine of herpes simplex virus of Long, et al, would be effective in enhancing the neutralizing antibody response to glycoprotein D, resulting in protection against infection with herpes virus types 1 and 2. The use of a particular ratio of QS-21 to 3D-MPL is well within the level of skill in the art, would be a matter of empirical determination and design choice.

23. Claims 1, 3 and 4 are rejected under 35 U.S.C. § 103 as being unpatentable over Schofield et al, 1987 or Weiss et al, 1988 in view of Kensil et al, U.S. Pat. No. 5,057,540 and further in view of Schneerson et al, 1991. Schofield et al describe the immunization of rats with irradiated *Plasmodium berghei* sporozoites. The immunization with irradiated

sporozoites generated humoral immunity as well as cell mediated immunity with the development of gamma interferon producing (γIFN) cytotoxic T cells, indicating the involvement of cytotoxic cells and γIFN in the development of immunity to malaria sporozoites (page 668). Likewise, Weiss et al describe immunization of mice with live sporozoites and the development of T cell-mediated immunity (abstract, page 573 and tables 1-3). Schofield, et al and Weiss et al differ from the claimed invention in not specifically describing antigenic compositions comprising QS-21 and 3D-MPL. However, the teachings of Kensil et al and Schneerson et al have already been described above. Thus it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include 3D-MPL and QS-21 in an antigenic composition of live or irradiated sporozoites. It would have been expected, barring evidence to the contrary, that the antigenic composition would generate enhanced cytolytic T cell responses and γIFN production which would result in enhanced immunity to malaria sporozoites.

24. Claims 1, 7, 9 and 11 are rejected under 35 U.S.C. § 103 as being unpatentable over Cantrell, U.S. Pat. No. 4,877,611 in view of Kensil et al, U.S. Pat. No. 5,057,540. Cantrell describes vaccines comprising adjuvants, such as MPL, together with tumor antigens. The MPL appears to be similar or an obvious or analogous variant of the claimed 3D-MPL (abstract and cols. 3-

6). It is stated that the vaccines are effective for the treatment and prevention of cancerous tumors (col. 2, lines 41-60) and can be used to provide a protective and lasting tumor immunity (abstract, col. 10-15). It is suggested that other adjuvants can also be employed with the immunogenic compositions (col. 5, lines 34-42). Cantrell differs from the claimed invention in not specifically describing the use of QS-21 in the anti-tumor composition. However, the teachings of Kensil et al, have already been described above. Thus it would have been *prima facie* obvious to one or ordinary skill in the art at the time the invention was made to include QS-21 and MPL in an anti-tumor antigenic composition. It would have been expected, barring evidence to the contrary, that the amount of anti-tumor composition administered would be safe and effective and would enhance tumor immunity which would be protective and long lasting.

25. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Lynette F. Smith, Art Unit 1813 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1813 FAX telephone number is (703)-305-7939. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission

will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynette F. Smith whose telephone number is (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Smith/lfs
July 19, 1995

L. F. Smith
Lynette F. Smith
Patent Examiner
Group 1800